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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
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ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/152,698	Madiyalakan et al
Examiner	**Art Unit**
Karen Canella	1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3 months* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☐ Responsive to communication(s) filed on _____.

2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *30, 31, 61-63, 67, and 69-97* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☒ Claim(s) *72, 81, and 90* is/are allowed.

6) ☒ Claim(s) *30, 31, 61-63, 67, 69-71, 73-80, 82-89, and 91-97* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 6
18) ☐ Interview Summary (PTO-413) Paper No(s). _____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

1. Please note that the examiner assigned to this application has changed.

2. Acknowledgment is made of applicants election with traverse of Group V, drawn to a composition comprising modified antigens. The traversal is on the grounds that the restriction is improper as it separates inventions co-extensive in subject matter. After examination of this application, the arguments presented by applicant are found persuasive. All pending claims will be examined at this time.

3. Claims 1-29, 32-60, 64, 65 and 68 have been canceled. Claims 71-97 have been added. Claims 30, 31, 61-63, 66, 67 and 69-97 are pending and examined on the merits.

Specification

4. The abstract of the disclosure is objected to because it fails to adequately summarize the instant invention. Correction is required. See MPEP § 608.01(b).

Oath/Declaration

5. The new declaration, filed January 7, 2002, is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

It was not executed in accordance with either 37 CFR 1.66 or 1.68.

Acknowledgment is made of applicants stated intention of filing an executed oath.

Priority

6. Acknowledgment is made of applicants claim to PCT/IB96/00461, filed May 15, 1996; 08/913,290, filed May 15, 1996; 08/877,511, filed June 17, 1997 and 09/094,598, filed June 15, 1998. However, the inventions of newly added claims 74, 83 and 92 are not disclosed in any of

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6/15/98
Check 09/094,598
pg 26, 28, 56, 72 fig 17
claim 48

the parent applications and will be thus given the priority date based on the instant filing date of September 2, 1998. Further, the photoactivated antibody of claims 72, 81, 90 was disclosed only in application 08/877,511, filed June 17, 1997, but not in the earlier applications, therefore claims 72, 81 and 90 will be given the priority date of June 17, 1997.

Claim Objections

7. Claim 31 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 31 is drawn to an antigen which is complementary to the structure of the antibody that binds to the exposed epitope. However, claim 30 is drawn to a method wherein the host is allowed to generate "an antibody that binds to the exposed epitope". As claim 30 is limited to the generation of a single antibody versus the induction of the idiotypic network, the antibody which binds the exposed epitope of claim 30 must be complementary to the antigen. Therefore, dependent claim 31 does not further limit claim 30.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 66, 67, 69, 70 and 87-89 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(A)Claim 66 and 67 recite: "composition....that induces the production of AB3 and AB3'". Claim 70 recites: "production of at least one of the following.....Ab3, Ab3'". The specification

uses Ab3 and Ab3' as a name for anti-anti-idiotypic antibodies as well as the pathway by which said antibodies are generated, therefore it unclear if AB3, AB3, Ab3 and Ab3' represent antibodies or methods of generating antibodies. Also the difference between **AB** vs **Ab** is unclear, and undefined by the specification.

(B)Claim 70 recites: "comprehensive method for killing cells". How a "comprehensive" method for killing cells differs from a method for killing cells is unclear. Claim 70 recites: "antibody that induces the production of at least one of the following: molecules associated with a cellular response, molecules associated with a humoral response, Ab3, Ab3', ADCC, CDC, cytotoxic T lymphocytes, natural killer cells, cytokines and chemokines". The metes and bonds of the claim are unclear because the effects of the antibody include both the production of specific molecules and the initiation of biological phenomenon such as ADCC, CDC and potentially Ab3 and Ab3' pathways.

(C)Claim 69 recites: "beneficial effect" without reference to the object that will benefit from said claimed beneficial effect.

(D)Claim 67 sets forth active method steps, but fails to state a method objective.

(E)The recitation of "antibody" in claim 87 lacks antecedent basis in claim 85.

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 74, 83 and 92 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had

possession of the claimed invention. Claims 74, 83 and 92 are drawn to compositions for altering immunogenicity comprising a modified antigen, wherein the antigen is associated with the human diseases or conditions selected from the group consisting of cancer, tumor, drugs of abuse, multiple sclerosis, allergy, human immunodeficiency virus, bacterial infection, autoimmune disease, human viruses and asthma. There is no support in either the specification or the originally filed claims for the treatment of drug abuse, multiple sclerosis, allergy, autoimmune disease or asthma , therefore, claims 74, 83 and 92 are rejected as introducing new matter into the specification.

12. Claims 79, 80, 88 and 89 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claims 79, 80, 88 and 89 are drawn in part to the specific monoclonal antibodies of B43.13 and AR20.5. There is no evidence in the specification that the claimed biological materials are readily available to the public. Neither is there evidence of the deposit of the biological materials.

The specification lacks deposit information for the deposit of the hybridoma cell lines producing the monoclonal antibodies designated B43.13 and AR20.5 It is not clear that monoclonal antibodies possessing the identical properties of B43.13 and AR20.5 are publicly available or can be reproducibly isolated from nature without undue experimentation.

Exact replication of a cell line is an unpredictable event. Clark (Protein Engineering of Antibody Molecules for Prophylactic and therapeutic Applications in Man, 1993, page 1) states "The in vivo antibody response is heterogeneous and is made up of a large mixture of antibodies secreted from a polyclonal population of cells. In addition, because the differentiation of B cells involves the random rearrangements of gene segments and somatic mutation of these rearranged genes,....no two animals, even of an inbred strain will make an identical set of antibodies." It is

unclear that one of skill in the art could derive antibodies and hybridomas identical to those claimed. Undue experimentation would be required to generate and screen all of the possible antibody and hybridoma species to obtained the claimed antibodies.

If deposits are made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney or record who has the authority and control over the conditions of deposit over his/her signature or registration number stating that the deposit has been accepted by an International Depository authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposits will be irrevocably removed upon the grant of a patent on this application and that the deposit will be replaced if viable samples cannot be dispensed from the depository as required. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

If deposits are not made under the provisions of the Budapest Treaty, then in order to certify that the deposits comply with the criteria set forth in 37 CFR 1.801-1.809 regarding availability and permanency of deposits, assurance of compliance is required. Such assurance may be in the form of an affidavit or declaration by applicants or assignees or in the form of a statement by an attorney of record who has the authority and control over the conditions of deposit over his or her signature and registration number averring:

(a) during the pendency of this application, access to the deposits will be afforded to the Commissioner upon request:

(b) all restrictions upon the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application:

© the deposits will be maintained in a public depository for a period of at least thirty years from the date of deposit or for the enforceable life of the patent of or for a period of five years after the date of the most recent request for the furnishing of a sample of the deposited biological material, whichever is longest; and

(d) the deposits will be replaced if they should become nonviable or non-replicable.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If deposits are made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to corroborate that the deposited hybridomas are producing the monoclonal antibody 1A3.3.13 as described in the specification as filed and are the same as those deposited in the depository, stating that the deposited hybridoma is producing the identical monoclonal antibody 1A3.3.13 as described in the specification and were in the applicant's possession at the time the application was filed.

Applicant's attention is directed to In re: Lundak, 773 F. 2d.1216, 227 USPQ 90 (CAFC 1985) and 37 CRF 1.801-1.809 for further information concerning deposit practice.

Claim Rejections - 35 USC § 102

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

14. Claims 30, 31, 61, 62, 63, 71, 73, 74, 77, 78, 85, 86, 87, 91, 92, 94, 95 and 97 are rejected under 35 U.S.C. 102(b) as being anticipated by Morgan et al (US 4,879,225). Claims 30 and 31 are drawn to a method of stimulating the production of antibodies that bind to an epitope on a soluble antigen comprising administering to a host a binding agent that binds to the soluble

antigen, forming a complex between the binding agent and the soluble antigen, wherein the formation of the complex exposes an epitope that is unexposed when the binding agent is not complexed to the antigen, and allowing the host to generate an antibody that binds to the exposed epitope. Claim 61 is drawn to a composition for altering immunogenicity comprising a modified antigen, said modified antigen comprising an antigen bound to a binding agent. Claim 61 embodies a soluble antigen. Claim 63 embodies a multi-epitopic antigen. Claims 71 and 77 embody the binding agent as an antibody and a monoclonal antibody. Claim 73 specifies the soluble agent as associated with human disease or condition. Claim 74 embodies cancer and tumor in part. Claim 78 specifies the binding agent as a monoclonal antibody. Claim 85 is drawn to a composition for altering immunogenicity comprising an antigen and a binding agent that specifically binds to the antigen, wherein the binding agent and the antigen form a complex, wherein the administration of the composition to the host alters the host immune response to the antigen. Claim 86 embodies a binding agent as an antibody and a monoclonal antibody. Claim 87 specifies the antibody as a monoclonal antibody. Claim 91 specifies that the antigen is associated with a human disease or condition. Claim 92 specifies in part that the human disease or condition is cancer or a tumor. Claim 94 embodies a multi-epitopic antigen. Claim 95 embodies a soluble antigen. Claim 97 specifies the exposing of a previously inaccessible epitope on the antigen after binding by the first antibody.

Morgan et al disclose a method for the enhanced production of antibodies using immune complexes consisting of pre-formed antibody-antigen complexes injected into a host, wherein the host generates antibodies to the epitopes on the antigen which are not masked in the antibody-antigen complex (column 6, lines 55-59). Morgan et al disclose that the method is an improvement in the prior art for generating antibodies to soluble immunogens which are weakly immunogenic (column 3, line 58 to column 4, line 3 and column 6, lines 47-51). Morgan et al disclose that the method provides a way to generate monoclonal antibodies against a multi-epitopic antigen (column 3, lines 28-31). Morgan et al do not specifically disclose that this

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method would generate antibodies to cryptic epitopes, however, antibodies to said cryptic epitopes would not be excluded by this method as all epitopes not masked in the first antibody-antigen complex would be available as antigenic epitopes in the host. Further, Morgan et al disclose that this method is useful for generating monoclonal antibodies directed to tumor-associated epitopes of non-tumor associated antigens. Thus Morgan et al disclose a method for the generation of antibodies to soluble antigens, multi-epitopic antigens and a method for the discovery of novel epitopes on tumor antigens which is commensurate with the unmasking of a cryptic epitope on a tumor associated or other antigen.

15. Claims 30, 31, 67, 69, 71, and 73-76 are rejected under 35 U.S.C. 102(b) as being anticipated by Koprowski et al (US 5,053,224) as evidenced by Chattopadhyay et al (Cancer research, 1991, Vol.51, pp. 6045-6051) and Rooijen (Res Immunol, 1993, Vol. 144, pp. 545-552).

Claims 30 and 31 are drawn to a method of stimulating the production of antibodies that bind to an epitope on a soluble antigen comprising administering to a host a binding agent that binds to the soluble antigen, forming a complex between the binding agent and the soluble antigen, wherein the formation of the complex exposes an epitope that is unexposed when the binding agent is not complexed to the antigen, and allowing the host to generate an antibody that binds to the exposed epitope. Claim 67 is drawn to a method of using a binding agent comprising administering a composition comprising a binding agent to induce the production of Ab3 and Ab3'. Claim 69 is drawn to a method of stimulating the production of antibodies which bind to an epitope on a soluble antigen comprising administering a monoclonal antibody the specifically binds to a soluble antigen in an amount sufficient to produce anti-anti-idiotypic antibodies that immunoreact with the antibody-antigen complex, wherein the production of anti-anti-idiotypic antibodies provides a beneficial effect. Claims 71 embodies the binding agent as an antibody and a monoclonal antibody. Claim 73 specifies the soluble agent as associated with human disease or

condition. Claim 74 embodies cancer and tumor in part. Claim 75 specifies gastro-intestinal cancer in part. Claim 76 embodies a human host.

Koprowski et al disclose a method of stimulating the production of antibodies which bind to an epitope on a solid tumor cell comprising administering a monoclonal anti-idiotypic antibody to a human in an amount sufficient to stimulate the production of anti-anti-idiotypic antibodies which immunoreact with said solid tumor cell epitope, wherein said monoclonal anti-idiotypic antibody immunoreacts through its paratope with a monoclonal antibody specific for said solid tumor cell epitope. Koprowski et al specifically disclose the monoconal antibodies 17-1A, C42032 and C41472 which bind to human gastrointestinal cells. Thus Koprowski et al disclose monoclonal antibodies as soluble antigens and anti-idiotypic antibodies as binding agents and the generation of anti-anti-idiotypic antibodies in the human host. Koprowski et al do not specifically disclose that the complex consisting of the anti-idiotypic antibody and the monoclonal antibody specific for the tumor cell epitope exposes an epitope on the monoclonal antibody, and allows the host to generate an antibody which binds to the exposed epitope, nor that the resulting anti-anti-idiotypic antibodies immunoreact with the complex of antibody/anti-idiotypic antibody (Ab3' versus Ab3). However the claimed embodiments of exposing a new epitope allowing the host to generate an anti-anti-idiotypic antibody which binds to a different epitope from the original Ab1 and the production of anti-anti-idiotypic antibodies which immunoreact with the complex of the antibody and anti-idiotypic antibody, versus the anti-idiotypic antibody alone, is inherent in the disclosed method as evidenced by Rooijen and Chattopadhyay et al.

Rooijen discloses that antibody/anti-idiotypic antibody complexes are transported, trapped and retained in follicular dendritic cells. Rooijen discloses that anti-idiotypic antibodies retained the follicles are subject to cyclical exposition of antigenic determinants by association and re-association with the antibodies present in the follicles and are thus involved in the selective activation of germinal B cell centers. Thus Rooijen discloses that antigenic determinants on anti-idiotypic antibodies which are not masked by association with Ab1 direct the activation of

germinal centers and antibody production (page 548-549, under "Antiidiotypic antibodies and idiotypic networks in the follicles").

Chattopadhyay et al disclose that the anti-idiotypic antibody, mAb IMEL-1 directed toward the idiotype of the monoclonal antibody, anti-HMW-MAA 225.28, induces anti-anti-idiotypic antibodies that bind the antigen HMW-MAA, but recognize epitopes which are distinct from the epitope recognized by anti-HMW-MAA 225.28 antibody. Chattopadhyay et al disclose that mAb IMEL-1 activates B-cell clones with a specificity which is different from that of the original antigen HMW-MAA. Chattopadhyay et al postulate that anti-idiotypic antibodies mimic the original antigenic epitope in an imperfect way, and as such can activate B-cell clone able to bind to the self-tumor antigen, but which has not been deleted due to self-reactiveness (page 6050, first column, lines 30 to 35).

Thus by the disclosures of Rooijen and Chattopadhyay et al it one of skill in the art can conclude that it is inherent in the idiotypic network that anti-anti-idiotypic antibodies will be generated that differ in epitope specificity from Ab1 and result in the breaking of self-tolerance and the activation of B-cell clones. Thus the method disclosed by Koprowski et al encompasses the generation of anti-anti-idiotype antibodies which do not bind to the original antigen at the same epitope as Ab1.

16. Claims 61 and 62 are rejected under 35 U.S.C. 102(b) as being anticipated by Klaus (Nature, 1978, Vol. 272, pp. 265-266). Claim 61 is drawn to a composition for altering immunogenicity comprising a modified antigen, said modified antigen comprising an antigen bound to a binding agent. Claim 62 specifies that the antigen is soluble. Klaus et al teach that compositions comprising antibody-antigen complexes are more effective at inducing an immune response to the antigen than the antigen alone. Klaus et al disclosed the particular antigen as dinitrophenylated hemocyanin, which is a soluble antigen.

103 on Koprowski and Rooijen in support of foreign

61 amended 112 ¶2 and ?

17. Claims 66, 67 and 69 are rejected under 35 U.S.C. 102(e) as anticipated by Raso et al (US 6,140,091). Claim 66 is drawn to a method of altering immunogenicity comprising administering a composition comprising a binding agent that induces the production of AB3 and AB3' and permitting said binding agent to specifically bind to a soluble antigen. Claim 67 is drawn to a method of using a binding agent comprising administering a composition comprising a binding agent and allowing the binding agent to induce the production of AB3 and AB3'. Claim 69 is drawn to a method of stimulating the production of antibodies which bind to an epitope on a soluble antigen comprising administering a monoclonal antibody that specifically binds to a soluble antigen in an amount sufficient to stimulate the production of anti-anti-idiotypic antibodies, wherein the production of anti-anti-idiotypic antibodies provides a beneficial effect. Raso et al disclose a method for the generation of antibodies which neutralize the soluble antigen of cocaine by the administration of an Ab1 antibody and the induction of an anti-idiotypic network thereby. Raso et al do specifically differentiate between AB3 versus AB3', however, the induction of AB3' would be inherent in the disclosed method as the antigen-antibody complex would be available as a discreet antigenic target, as the cocaine antigen is present as a soluble antigen in the blood.

18. Claim 69 is rejected under 35 U.S.C. 102(b) as being anticipated by Madiyalakan et al (Hybridoma, 1994, Vol. 14, pp. 199-203, reference A2 of the IDS filed March 20, 2000) as evidenced by either of Tassi et al (Immunology Letters, 1991, Vol. 27, pp. 39-44) or Frodin et al (Hybridoma, 1991, Vol. 10, pp. 421-431) or Fagerberg et al (Cancer Immunol Immunother, 1996, Vol. 42, pp. 81-87).

Claim 69 is drawn to a method of stimulating the production of antibodies which bind to an epitope on a soluble antigen comprising administering a monoclonal antibody that specifically binds to a soluble antigen in an amount sufficient to stimulate the production of anti-anti-idiotypic antibodies, wherein the production of anti-anti-idiotypic antibodies provides a beneficial effect.

maintain

Madiyalakan et al disclose the administration of a monoclonal antibody, Mab43.13, which induces the anti-anti-idiotypic antibodies in patients having circulating tumor antigen CA125 in the serum. Thus Madiyalakan et al disclose a method comprising the administration of a monoclonal antibody which binds to a soluble antigen in an amount sufficient to prolong the survival time in patients. Madiyalakan et al disclose that anti-idiotypic and anti-anti-idiotypic antibodies were generated in patients having circulating tumor antigen. Madiyalakan et al do not specifically disclose that anti-anti-idiotypic antibodies versus the anti-idiotypic antibodies were correlated with prolonged survival time in patients.

Either of Tassi et al or Frodin et al or Fagerberg et al disclose that the development of an anti-anti-idiotypic response is associated with the development of anti-tumor immunity.

Based on this knowledge, it would be reasonable to assume that in the method disclosed by Madiyalakan et al, the production of anti-anti-idiotypic antibodies correlated with prolonged survival times.

19. Claim 61 is rejected under 35 U.S.C. 102(e) as being anticipated by either Zanetti (US 5,583,202). Claim 61 is drawn to a composition for altering immunogenicity comprising a modified antigen, said modified antigen comprising an antigen bound to a binding agent. Zanetti discloses antigenized antibodies comprising an antigen covalently bound to the framework region of an antibody. As it is well known in the art that the framework region of an antibody is a ligand for Fc receptors on effector and antigen-presenting cells (see: dictionary of Immunology, Herbert, Ed., 1985, page 79, Fc-receptors), and, as the claim language encompasses antigens covalently bound to other proteins as well as antigens complexed with other proteins, the molecules disclosed by Zanetti represent modified antigens with the Fc region of the antibody representing the binding agent. Zanetti also teaches that the disclosed molecules are useful for building tolerance to certain antigens, especially those associated with autoimmune disease, and for providing passive immunity against pathogenic antigens (column 3).

wd on "foreign"

20. Claim 70 is rejected under 35 U.S.C. 102(b) as being anticipated by any of Madiyalakan et al (Hybridoma, 1994, Vol. 14, pp. 199-203, reference A2 of the IDS filed March 20, 2000) or Fagerberg et al (Cancer Immunol Imunother, 1996, Vol. 42, pp. 81-87) or Frodin et al (Hybridoma, 1991, vol. 10, pp. 421-431) or Tsang et al (US 5,688,657) or Chu et al (US 5,652,114) or Sclom (In: Molecular foundations of Oncology, 1991, pp. 105-107). Claim 70 is drawn to a method for killing cells comprising administering a composition comprising an Ab1 antibody that induces the production of one of the following: Ab3, Ab3', ADCC, CDC, cytotoxic T-cells, lymphocytes, natural killer cells, cytokines and cheomkines.

Madiyalakan et al discloses a method for killing tumor cells comprising the administration of monoclonal antibody B43.13 and the induction of anti-anti-idiotypic antibodies.

Frodin et al and Fagerberg et al disclose a method for killing tumor cells comprising the administration of the monoclonal antibody 17-1A and the induction of anti-anti-idiotypic antibodies.

Chu et al disclose a method for killing tumor cells comprising the administration of Mab F36/22 and the induction of CDC.

Tsang et al disclose a method for killing tumor cells comprising the administration of monoclonal antibodies 33.28 or 31.1 and the induction of ADCC and CDC.

Schlom reviews methods of killing tumor cells comprising the administration of non-conjugated monoclonal antibodies inducing ADCC, CDC and the anti-idiotypic network.

Claim Rejections - 35 USC § 103

21. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

22. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

23. Claims 61-63, 77, 78, 79, 82-88, 91, 92, 93, 94, 95 and 96 are rejected under 35 U.S.C. 103(a) as being unpatentable over Madiyalakan et al (Hybridoma, 1994, Vol. 14, pp. 199-203, reference A2 of the IDS filed March 20, 2000) in view of Klaus (Nature, 1978, Vol. 272, pp. 265-266). Claim 61 is drawn to a composition for altering immunogenicity comprising a modified antigen, said modified antigen comprising an antigen bound to a binding agent. Claims 62 and 63 embody a soluble antigen and a multi-epitopic antigen, respectively. Claim 77 specifies in part that the binding agent is an antibody, a monoclonal antibody and a protein. Claims 78 and 79 specify a monoclonal antibody and B43.13, respectively. Claims 82 and 83 embody a human disease or condition and cancer and tumors, respectively. Claim 84 specifies in part ovarian cancers. Claim 85 is drawn to a composition for altering immunogenicity comprising an antigen and a binding agent which specifically binds to the antigen, wherein the binding agent and the antigen form a complex, and wherein the administration of the composition to the host alters the host immune response against the antigen.. Claim 86 is drawn in part to the binding agent as a member of an immunologic pair, an antibody, a monoclonal antibody and a protein. Claim 87 specifies a monoclonal antibody. Claim 88 specifies the monoclonal antibody of B43.13. Claim 91 embodies the antigen as associated with a human disease or condition. Claim 92 is drawn in part to cancer and tumors. Claim 93 further specifies ovarian cancer. Claims 94 and 95 specify

that the antigen is multi-epitopic and soluble, respectively. Claim 96 embodies the host as a human.

Claim 66 is drawn to a method of altering immunogenicity comprising administering a composition comprising a binding agent that induces the production of AB3 and AB3', and permitting said binding agent to specifically bind to a soluble antigen. Claim 67 id drawn to the use of a binding agent for the induction of Ab3 and AB3'.

Madiyalakan et al teach the administration of a composition comprising the monoclonal antibody, Mab43.13, to patients having ovarian cancer. Madiyalakan et al teach that Mab43.13 induces the anti-idiotypic network, as exemplified by the presence of anti-idiotypic antibodies and anti-anti-idiotypic antibodies, in patients having circulating tumor antigen CA125 in the serum. Thus Madiyalakan et al teach a method comprising the administration of a monoclonal antibody which binds to a soluble antigen in an amount sufficient to prolong the survival time in patients as it would be inherent that the administered monoclonal antibody would bind to the CA125 antigen in the serum of patients. Madiyalakan et al disclose that anti-idiotypic network was dependent on patients having circulating tumor antigen. Madiyalakan et al do not teach a composition comprising a complex of Mab43.13 and CA-125 or the induction of AB3'.

Klaus teaches compositions comprising antibody-antigen complexes are more effective at generating anti-idiotypic antibodies than the antibody alone.

It would have been *prima facia* obvious to one of ordinary skill in the art at the time the claimed invention was made to administer the Mab43.13 antibody as a complex with the CA-125 antigen for the induction of AB3. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Klaus on the heightened ability of the immune system to generate anti-idiotypic antibodies when presented with an antibody-antigen complex, and by the teachings of Madiyalakan et al on the correlation between the induction of the anti-idiotypic network and prolonged survival times in ovarian cancer patients. Further, with the induction of AB3 in the presence of the antigen, it would be inherent that the

AB3' pathway would also be induced as the CA-125 antigen complexed with the Mab43.13 antibody will represent a discreet antigenic target.

24. Claims 61, 63, 77, 78, 82, 83, 84, 85, 86, 87, 91, 92, 93, 94 and 96 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fagerberg et al (Cancer Immunol Imunother, 1996, Vol. 42, pp. 81-87) or Frodin et al (Hybridoma, 1991, vol. 10, pp. 421-431) or Tsang et al (US 5,688,657) or Chu et al (US 5,652,114) in view of Klaus (Nature, 1978, Vol. 272, pp. 265-266).

Claim 61 is drawn to a composition for altering immunogenicity comprising an antigen bound to a binding agent. Claim 63 embodies a multi-epitopic antigen. Claim 77 specifies in part that the binding agent is an antibody, a monoclonal antibody and a protein. Claim 78 specifies a monoclonal antibody. Claims 82 and 83 embody a human disease or condition and cancer and tumors, respectively. Claim 84 specifies in part breast tumors and gastro-intestinal tumors. Claim 85 is drawn to a composition for altering immunogenicity comprising an antigen and a binding agent which specifically binds to the antigen, wherein the binding agent and the antigen form a complex, and wherein the administration of the composition to the host alters the host immune response against the antigen.. Claim 86 is drawn in part to the binding agent as a member of an immunologic pair, an antibody, a monoclonal antibody and a protein. Claim 87 specifies a monoclonal antibody. Claim 91 embodies the antigen as associated with a human disease or condition. Claim 92 is drawn in part to cancer and tumors. Claim 93 further specifies breast and gastrointestinal cancers. Claims 94 specifies that the antigen is multi-epitopic. Claim 96 embodies the host as a human.

Frodin et al and Fagerberg et al teach a method inducing passive immunity to tumor cells comprising the administration of a composition comprising the monoclonal antibody 17-1A directed toward the multi-epitopic gastrointestinal tumor antigen CA125

Chu et al teach a method for inducing passive immunity against breast tumor cells comprising the administration of a composition comprising Mab F36/22 directed toward the multi-epitopic ductal carcinoma antigen..

Tsang et al teach a method for inducing passive immunity against colon breast and ovarian tumor cells comprising the administration of a composition comprising monoclonal antibodies and chimeric antibodies directed toward a multi-epitopic glycoprotein antigen.

Neither Frodin et al nor Fagerberg et al nor Chu et al, nor Tsang et al teach a composition comprising a tumor antigen complexed to a monoclonal antibody.

Klaus et al teach that compositions comprising antibody-antigen complexes are more effective in comparison to antigen alone for the generation of an immune response against antigen and the induction of an anti-idiotypic network.

It would have been *prima facia* obvious to one of ordinary skill in the art at the time the claimed invention was made to administer the anti-tumor monoclonal antibodies taught by Frodin et al or Fagerberg et al or Chu et al or Tsang et al as compositions comprising anti-tumor monoclonal antibodies complexed with the tumor antigens that said antibodies are directed to. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Klaus on the heightened immune response to antigen effected by immunization with antigen-antibody complexes versus antigen alone.

25. Claims 66, 67, 69 and 70 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fagerberg et al (Cancer Immunol Imunother, 1996, Vol. 42, pp. 81-87) or Frodin et al (Hybridoma, 1991, vol. 10, pp. 421-431) or Tsang et al (US 5,688,657) or Chu et al (US 5,652,114) in view of Klaus (Nature, 1978, Vol. 272, pp. 265-266) as applied to the composition claims 61, 63, 77, 78, 82, 83, 84, 85, 86, 87, 91, 92, 93, 94 and 96 above, and further in view of Tassi et al (Immunology Letters, 1991, Vol. 27, pp. 39-44) or Frodin et al (Hybridoma, 1991, Vol. 10, pp. 421-431) or Fagerberg et al (Cancer Immunol Immunother, 1996, Vol. 42, pp. 81-

87). Claim 66 is drawn to a method of altering immunogenicity comprising administering a composition comprising a binding agent that induces the production of AB3 and AB3' and permitting said binding agent to specifically bind to a soluble antigen. Claim 67 is drawn to a method of using a binding agent comprising administering a composition comprising a binding agent and allowing the binding agent to induce the production of AB3 and AB3'. Claim 69 is drawn to a method of stimulating the production of antibodies which bind to an epitope on a soluble antigen comprising administering a monoclonal antibody that specifically binds to a soluble antigen in an amount sufficient to stimulate the production of anti-anti-idiotypic antibodies, wherein the production of anti-anti-idiotypic antibodies provides a beneficial effect. Claim 70 is drawn to a method for killing cells comprising administering a composition comprising an Ab1 antibody that induces the production of one of the following: Ab3, Ab3', ADCC, CDC, cytotoxic T-cells, lymphocytes, natural killer cells, cytokines and cheomkines. For the reasons set forth in the paragraph supra, Fagerberg et al or Frodin et al or Tsang et al in view of Klaus renders obvious a composition comprising a tumor antigen complexed to an anti-tumor antigen antibody in the treatment of breast, ovarian and gastrointestinal cancers and tumors. However, neither Fagerberg et al or Frodin et al or Tsang et al nor Klaus teach a method for altering immunogenicity comprising administering a composition comprising a binding agent that induces the production of AB3 and AB3', nor a method of stimulating the production of anti-anti-idiotypic antibodies.

Either of Tassi et al or Frodin et al or Fagerberg et al disclose that the development of an anti-anti-idiotypic response is associated with the development of anti-tumor immunity.

It would have been *prima facia* obvious to one of ordinary skill in the art at the time the claimed invention was made to administer a composition comprising tumor antigen-complexed with anti-tumor antigen antibodies in an amount sufficient to generate anti-anti-idiotypic antibodies. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of either of Tassi et al or Frodin et al or Fagerberg et al

the association between the development of an anti-anti-idiotypic response and the development of anti-tumor immunity. Further, with the induction of AB3 in the presence of the antigen, it would be inherent that the AB3' pathway would also be induced as the tumor antigen complexed with the anti-tumor antigen antibody will represent a discreet antigenic target.

Double Patenting

26. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

27. Claims 30, 31, 61-63, 66, 67, 69-71, 73-80, 82-89, 91-97 are rejected under the judicially created doctrine of double patenting over claims 1-14 of U. S. Patent No. 6,241,985 since the claims, if allowed, would improperly extend the "right to exclude" already granted in the patent.

The subject matter claimed in the instant application is fully disclosed in the patent and is covered by the patent since the patent and the application are claiming common subject matter, as follows: the invention of compositions in which a binding agent to a pre-determined epitope of a multi-epitopic tumor assoicated antigen alters the antigen in such a way so that the host immune system can recognize said altered antigen as non-self and initiate an immune response. Further it is disclosed that the predominant mechanism of a response aginst the new epitope is the Pathway II which is idnetical to the AB3' pathway disclosed herein.

Furthermore, there is no apparent reason why applicant was prevented from presenting claims corresponding to those of the instant application during prosecution of the application which matured into a patent. See *In re Schneller*, 397 F.2d 350, 158 USPQ 210 (CCPA 1968). See also MPEP § 804.

28. Claims 72, 81 and 90 are rejected under the judicially created doctrine of double patenting over claims 1-5 of U. S. Patent No. 6,086,873 since the claims, if allowed, would improperly extend the "right to exclude" already granted in the patent.

The subject matter claimed in the instant application is fully disclosed in the patent and is covered by the patent since the patent and the application are claiming common subject matter, as follows: a method for inducing a heightened immune response to an antigen by administering a photoactivated antibody to said antigen was disclosed in the '873 patent.

Furthermore, there is no apparent reason why applicant was prevented from presenting claims corresponding to those of the instant application during prosecution of the application which matured into a patent. See *In re Schneller*, 397 F.2d 350, 158 USPQ 210 (CCPA 1968). See also MPEP § 804.

Conclusion

29. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Karen A. Canella, Ph.D.

Patent Examiner, Group 1642

February 24, 2002

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